

## **REMARKS**

### **Status of the Claims**

Currently claims 2-5, 11-22, and 24-32 are pending. Claims 16-19 and 25-32 were withdrawn as being drawn to nonelected inventions. Claim 2 is amended as described elsewhere herein without prejudice or disclaimer of the subject matter therein. Support for the amendments can be found in the original claims, throughout the specification, and as set forth herein below. Accordingly, no new subject matter is added.

### **Election/Restrictions**

Applicants have filed a Request for Continued Examination in the present application and are considering the pursuit of the withdrawn subject matter in a divisional application.

### **Provisional Nonstatutory Obviousness-type Double Patenting**

The Examiner has held the provisional obviousness-type double patenting rejections over USSN 10/533462 and USSN 11/587023 in abeyance. Upon notice of allowable subject matter in anyone of the cited cases, Applicants will consider the filing of terminal disclaimers or other appropriate action in this or the other pending cases.

### **The Rejection Under Section 103 Should be Withdrawn**

Claims 2-5, 11-15, 20-22, and 24 stand rejected under Section 103 for alleged obviousness over Boutriau, in view of Kurikka, in further view of Truong-Le, in further view of Volken, in further view of Roser. Applicants respectfully disagree.

In the previous office action (mailed 29 Apr 2008), it was stated:

It would have been obvious to one of ordinary skill in the art to modify the compositions taught by Boutriau et al. and Kurikka et al. in order to provide a dried multivalent vaccine of IPV and bacterial saccharides as a foamed glass composition with a stabilizing agent. One would have been motivated to do so, given the suggestion by Boutriau et al. and Kurikka et al., that the compositions be modified in order to incorporate the various antigens of interest into a stable vaccine composition with sucrose, a stabilizing agent followed by lyophilization

and that compositions such as that claimed be utilized in simultaneous vaccinations, respectively.

See page 6 of the 29 Apr 2008 office action.

In their response dated 4 Jun 2009, Applicants pointed out two major defects in the rejection:

Issue 1. The rejection failed to provide a rational underpinning to support its conclusion based on the cited references the skilled person would lyophilize Inactivated Poliomyelitis Vaccine (IPV).

Issue 2. The skilled person would have lacked a reasonable expectation of success for modifying the cited references to produce Applicants' claimed subject matter.

With respect to the first issue, Applicants pointed out that

- Boutriau *et al.* did not teach or suggest drying IPV;
- Kurikka did not teach or suggest a dried IPV, but rather discussed providing a monovalent IPV in liquid form; and
- the other references failed to make up these deficiencies.

Because there was no teaching or suggestion to dry IPV, the references cited in the previous rejection failed to establish a *prima facie* case of obviousness.

With respect to the second issue, Applicants pointed out that

- As of Applicants' priority date, "no successful example of making a dried solid vaccine formulation of IPV that retains a high degree of antigenicity and/or immunogenicity has been reported" (specification, page 3 lines 6-7); and
- "The process of freeze-drying IPV has been associated with the loss of antigenicity so that it is difficult to formulate an effective vaccine comprising a dried form of IPV." (specification, page 1, lines 15-18)

Although Applicants' representative diligently searched the references cited in the rejection, nothing could be found that contradicts the statements made in the Applicants' specification and pointed out by Applicants. Accordingly, the rejection failed to establish that the skilled person would have had a reasonable expectation of successfully modifying the cited references to produce the claimed invention.

The present rejection continues to rely on Boutriau *et al.* and Kurikka. For example, the rejection now asserts that Boutriau *et al.* discusses multivalent vaccine compositions that are lyophilized. But this misses the point that Boutriau *et al.* do not

teach or suggest lyophilized IPV combined with the Hib antigen. Rather, Boutriau *et al.* state: "Preferably the vaccine may be supplied in 2 containers, the first containing DTPw-HepB in a liquid form, and a second containing Hib-MenA-MenC in a lyophilized form." See Boutriau *et al.*, page 5. Whether or not Hib-MenA-MenC could be successfully lyophilized without loss of antigenicity is wholly irrelevant to the inquiry of whether the skilled person would have a reasonable expectation of success when lyophilizing IPV.

The rejection also relies upon Kurikka for the suggestion that compositions containing Hib and compositions containing IPV should be administered at the same time and that combining Boutriau *et al.* with Kurikka would lead the skilled person to make a lyophilized composition comprising IPV. But the study cited in Kurikka utilized a monovalent IPV and there was no mention of drying the IPV. Moreover, one could administer IPV and Hib at the same time without need to lyophilize IPV, for instance by reconstituting a dried Hib composition in liquid IPV. This would not motivate the skilled person to lyophilize IPV, nor would it provide a reasonable expectation of successfully lyophilizing IPV.

The rejection has introduced a new reference by Roser that allegedly demonstrates the successful production of lyophilized IPV, specifically in Example 3. However, after carefully reviewing this reference, one finds that Roser was lyophilizing whole poliovirus, not IPV (which comprises individual antigens from poliovirus). Whether or not one could lyophilize whole poliovirus without a damaging loss of activity is irrelevant to whether or not the skilled person would have a reasonable expectation of success when lyophilizing IPV. (Moreover, it should be noted that Roser reported a 2.9 log loss of cytopathic titre, a 1000-fold loss of whole-polio virus activity.) Thus, Roser fails to cure the deficiencies of the primary references.

With respect to Truong-Le, the rejection concedes that it fails to teach or suggest dried IPV. Office Action mailed 20 Aug 2009, page 7. The rejection goes on to allege that "...Truong-Le provide insight into the technology used for preparing IPV and other viruses for future applications." Applicants' representative admits some confusion regarding this statement, although it does not appear to contradict the earlier

concession that Truong-le fails to teach or suggest dried IPV. Truong-Le fails to cure the deficiencies of the other references.

With respect to Volkin *et al.*, the rejection now indicates that it was cited for the inclusion of phenol red to indicate pH changes in vaccine formulations. Applicants' representative requests clarification regarding how this relates to the claimed subject matter.

In the present rejection, it has been stated that "Applicants argue that Boutriau *et al.* do not provide working examples involving a combination of IPV, *N. meningitidis* and *H. influenzae*." The rejection then goes on to argue that a reference cited in support of obviousness can be considered enabling whether or not it contains a working example. See paragraph spanning page 5-6 of the Office Action mailed 20 Aug 09. This misses the point made in Applicants' previous response, namely that none of the references, alone or together, establish that the skilled person would have had a reasonable expectation of modifying the references to produce Applicants' claimed subject matter.

It is elemental that where, as here, a rejection alleges that the prior art can be modified or combined to reject claims as prima facie obvious, it must be established that there is a reasonable expectation of success. MPEP2143.02I. Furthermore, when, as here, an Applicant challenges a factual assertion, the Examiner must support the finding with adequate evidence. MPEP 2144.03(C). The Examiner bears the burden of producing a preponderance of evidence favoring his conclusion that the skilled person would have a reasonable expectation of success.

To further support a conclusion that the skilled person would have lacked the requisite reasonable expectation of success in producing Applicants' claimed subject matter, Applicants now submit two references by Information Disclosure Statement filed contemporaneously herewith:

**Exhibit A:** Nagel *et al.* (1962) *Archives of Virology* 12:718-720.

**Exhibit B:** Galazka (ed.) "Temperature sensitivity of vaccines." WHO/IVB/06.10, World Health Organization (2006), pp. 33-38.

As the reader will appreciate, the authors reported a significant loss of IPV antigenicity during the drying process. See Nagel *et al.*, published in 1962, reporting

on page 718 that lyophilization of inactivated poliovaccines led only to partial success and Galazka, printed over 40 years later, noting in the discussion of IPV on page 37 that “[t]he capacity of poliovirus to produce neutralizing antibodies is destroyed by heat treatment, freeze-drying and the addition of merthiolate....” These documents favor a conclusion that the skilled person would have lacked a reasonable expectation of success had they chosen to attempt to make a dried IPV component capable of generating an immune response against polio virus. These documents are the only evidence of record on this factual issue.

To emphasize that the rejection fails to establish a reasonable expectation of success, Applicants have amended the claims as described elsewhere herein. Support for the amendments can be found on page 6, lines 11-16 and on page 19, line 15. The Examiner's attention is drawn to Example 5, Table 4, which present the results of an experiment testing retention of IPV in a Hib-IPV composition formulated according to one of Applicants' disclosed processes.

Applicants' evidence of record supports a conclusion that the skilled person would not have had a reasonable expectation of successfully modifying or combining the cited references to produce Applicants' claimed invention. It is the Office's burden of establishing this conclusion in order to make a Section 103 obviousness rejection. Accordingly, the Office has not met its burden here and the present rejection must be withdrawn.

### **CONCLUSION**

Applicants submit that given the amendments and points of distinction set forth in the Remarks, this application is now in condition for allowance. Early notice to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

The Commissioner is hereby authorized to charge any fees required or credit any overpayment to Deposit Account No. 07-1392.

Respectfully submitted,

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